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Controlling isolated systolic hypertension

No time to be complacent

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CME learning objectives

- To understand the importance of **isolated systolic hypertension** as a cause of stroke and myocardial infarction, particularly in the elderly population
- To review the clinical trials documenting the importance of reducing elevated **systolic hypertension**
- To become familiar with the treatment of **isolated systolic hypertension**

This is the second of three articles on **hypertension**

This page is best viewed with a browser that supports tables

Preview: Elevated **systolic** blood pressure is often thought to be of less concern than elevated diastolic pressure, but study after study has refuted this belief. **Isolated systolic**

hypertension has proved to be an important cause of morbidity and mortality. Dr Pentz examines the causes and risks associated with this condition, touches on some of the important studies that have documented its seriousness, and offers practical advice on evaluation and treatment.

Isolated systolic hypertension (ISH) is defined as elevated **systolic** blood pressure in conjunction with normal diastolic blood pressure (<90 mm Hg). Previously, **systolic** pressure of more than 160 mm Hg was classified as ISH, and pressure between 140 and 160 mm Hg was classified as borderline ISH. In 1993 the definition of ISH was changed to any **systolic** blood pressure above 140 mm Hg together with diastolic blood pressure below 90 mm Hg (1). ISH is characterized by an increased pulse pressure, defined as the difference between the **systolic** and diastolic blood pressures.

Hypertension is present in more than half of all persons over 60 years of age, regardless of race (2). The majority of hypertensive patients in this age-group have ISH (3,4). Its prevalence increases with age, from about 5% of persons aged 60 years to almost 25% of those aged 80 years (5), and is higher in elderly women than in elderly men (6).

The number of elderly among the populations of the United States and many other countries is rising rapidly. At the beginning of the 20th century, only 4% of the US population was older than 65 years of age. By 2040, the comparable figure is estimated to be 21%. Clearly, therefore, ISH will be an important issue for practitioners in the years to come. A good understanding of the pathophysiology of ISH and the morbidity and mortality it causes will be crucial to successfully evaluating and treating this disease.

Why and how ISH develops

Many believe ISH to be a natural consequence of aging. However, no age-related increase in blood pressure is seen in relatively primitive societies whose members maintain lean body mass and are physically active. Factors that may play a role in the high prevalence of ISH seen in Western societies include increased body fat, sedentary lifestyle, and increased sodium intake (7).

One of the most important factors in the development of ISH is believed to be a loss of elasticity, and therefore of distensibility, of the aorta and peripheral arteries. Some compensation can be gained by dilatation of the aorta (8). An aorta with normal elastic properties is able to absorb much of the energy released during ventricular ejection, thereby attenuating the rise in **systolic** blood pressure. Histo-pathologic examination of the aorta of an elderly person in Western society typically reveals thickening of the aorta and media due to the accumulation of collagenous fibers, as well as calcium deposition (9).

Increased cardiac output may play a role in ISH (10). In addition, elderly hypertensive patients tend to have relatively low plasma volume and relatively low levels of

renin and aldosterone. Renal excretion of salt tends to be decreased in these patients, and this probably accounts for their relatively greater salt sensitivity compared with their younger counterparts (11). Decreased calcium levels resulting from increased calciuria and poor dietary intake may also increase peripheral resistance, leading to **hypertension** (7).

Risks associated with ISH

A common misconception among patients and some practitioners is that elevated diastolic blood pressure is more important than elevated **systolic** pressure. This misconception most likely stems from studies on **hypertension** done in the 1960s and 1970s in which diastolic blood pressure was used as a measure of the efficacy of treatment. In fact, elevated **systolic** blood pressure has consistently been shown to be a better predictor of cardiovascular events, including stroke and myocardial infarction (8).

A study of more than 22,000 male physicians revealed that ISH was associated with a significantly increased risk of stroke and cardiovascular death (12). In a 15-year follow-up of over 300,000 patients screened for the Multiple Risk Factor Intervention Trial, ISH was identified as an independent risk factor for end-stage renal disease (13). Numerous epidemiologic studies have shown that ISH increases the risk of stroke threefold. ISH is also associated with a significantly increased risk of overall mortality, cardiovascular mortality, and congestive heart failure (14).

The continued reliance solely on diastolic blood pressure readings is puzzling, given the abundant data revealing ISH to be a major cause of morbidity and mortality.

Clinical trials

Many physicians have been reluctant to treat ISH out of the mistaken belief that it is a benign condition and for fear that lowering **systolic** blood pressure will result in strokes, a decline in renal function, and impaired cognition. Although more emphasis has been placed on the morbidity and mortality of ISH in recent years, evidence from clinical trials showing that treatment of ISH reduces adverse outcomes did not become available until the early 1990s.

The SHEP trial

The **Systolic Hypertension** in the Elderly Program (SHEP) was the first large-scale trial to document a benefit from treatment of ISH. The 4,736 patients enrolled in this double-blind, randomized, placebo-controlled study were 60 years of age or older. Participants received stepped-care treatment with chlorthalidone, and atenolol was added to the regimen if the target blood pressure was not achieved with chlorthalidone alone. The goal was to reduce **systolic** pressure to less than 160 mm Hg in those with initial readings of more than 180 mm Hg and to reduce the **systolic** pressure by 20 mm Hg in those with initial readings between 160 and 180 mm Hg. The primary end point was the number of fatal and nonfatal strokes in patients receiving treatment versus those receiving placebo. Secondary end points were cardiac events and overall

mortality in these two groups.

Over a 5-year follow-up period, the SHEP trial showed an average **systolic** blood pressure of 155 mm Hg in patients taking placebo and 143 mm Hg in patients receiving medication. The overall results were very impressive. The number of strokes was reduced by 36% in the group receiving medication compared with the group receiving placebo. Analysis of secondary end points showed nonfatal myocardial infarctions plus death from cardiac causes to have been reduced by 27% and major cardiovascular events by 32%. The incidence of congestive heart failure was cut in half by treatment with medication. The 13% reduction in all-cause mortality among patients receiving medication did not reach statistical significance (figure 1: not shown) (15).

The Syst-Eur trial

The **Systolic Hypertension** in Europe (Syst-Eur) trial was conducted about the same time as the SHEP study, but results were published later. The 4,695 patients recruited for the study were over 60 years of age and had **systolic** pressures between 160 and 219 mm Hg and diastolic pressures below 95 mm Hg. Patients were randomly selected to receive the long-acting dihydropyridine calcium channel blocker nitrendipine or a placebo. If blood pressure was not optimally controlled, enalapril, hydrochlorothiazide, or both were added.

Over a 2-year follow-up period, patients receiving treatment had their **systolic** blood pressures lowered by an average of 10 mm Hg over the placebo group. The primary end point was fatal or nonfatal stroke. Active treatment reduced the number of total strokes by 42%, nonfatal strokes by 44%, and cardiac events by 26%. As in the SHEP study, total mortality was not reduced significantly by active treatment (16,17).

The STONE study

The Shanghai Trial of Nifedipine in the Elderly (STONE) was a study of the effects of long-acting nifedipine in elderly hypertensive patients aged 60 to 79 years. Here again, results showed medication to be superior to placebo. The risk of any cardiac or vascular event was reduced by 59% in the treatment group, mainly owing to a decreased risk of stroke or severe arrhythmia (18).

Implications of clinical trials

The SHEP and Syst-Eur trials provide strong evidence that treating ISH can significantly reduce the incidence of stroke, cardiac events,and congestive heart failure. Analysis of the Syst-Eur data indicates that for every 1,000 patients treated for 5 years, 29 strokes and 53 major cardiac events will be averted (17). This may represent an underestimate of the benefit of treatment, because the analysis includes patients who did not have blood pressure lowered to target goals with active treatment.

The Syst-Eur and STONE studies should reassure the practitioner that long-acting dihydropyridine calcium channel blockers are safe to use in the elderly and other populations at increased risk of adverse events, despite the negative publicity surrounding the short-acting calcium channel blockers.

Evaluation of the patient

Cases of ISH require careful attention to patient history, accurate assessment of blood pressure, and laboratory tests to identify concomitant medical problems.

History
The evaluation of a patient with ISH begins with a complete history. Details about the duration and severity of the **hypertension** should be elicited. Sudden onset of severe **hypertension** raises the suspicion of a secondary form of **hypertension**. Information about concomitant medical conditions must be obtained. Patients with a history of cardiac, renal, or vascular disease should have their blood pressure more aggressively controlled than patients without these conditions. Questions about dietary habits, alcohol consumption, tobacco use, and level of physical activity should be asked.

Details should be obtained about the medications that have been tried in the past, with particular attention to their side effects and efficacy in controlling blood pressure. Current medications, including over-the-counter preparations, must be thoroughly reviewed, remembering that elderly patients in many cases are taking multiple agents. Medications such as non-steroidal anti-inflammatory drugs (NSAIDs) can decrease the efficacy of many antihypertensives (19); it has been postulated that NSAID inhibition of prostaglandin synthesis is responsible. Certain prostaglandins are believed to antagonize the action of angiotensin II, which is a potent vasoconstrictor (20).

Physical examination
Precise measurement of blood pressure is essential, as there are many potential sources of error. The patient should be seated and comfortable. All outer garments must be removed from the arms. Use of the proper-sized cuff is essential, because one that is too small can cause falsely elevated blood pressure readings. The arms should be well supported, and measurements should be taken in both arms.

Blood pressure should be measured with the patient in both seated and standing positions. Elderly patients are at increased risk of orthostatic hypotension. Patients should be in a standing position for at least 1 minute, and preferably several minutes, before the measurement is taken. The SHEP trial documented orthostatic declines of more than 20 mm Hg in **systolic** blood pressure in 17% of the study group (19).

A funduscopic examination should be performed to assess for arteriovenous nicking, a sign of long-standing **hypertension**. Malignant **hypertension** may be characterized by papilledema. Palpation may reveal a displaced apical impulse, indicative of left ventricular dilatation. A sustained apical impulse may indicate left ventricular hypertrophy.

Auscultation should focus on listening for an S_4 or any murmurs indicative of coexisting valvular disease. Abdominal examination may reveal an enlarged and pulsatile aorta, which may indicate an abdominal aneurysm. A bruit

that lateralizes to one side of the abdomen should raise suspicion for renal arterial stenosis. Femoral and peripheral pulses should be palpated to assess for vascular disease.

Laboratory analysis

Laboratory tests should focus on assessment for concomitant medical problems as well as end-organ damage. A serum chemistry profile should be ordered to determine whether diabetes, renal disease, or hypokalemia is present. Chronic renal disease is the most common cause of secondary **hypertension** in the elderly. Unexplained hypokalemia should prompt suspicion for hyperaldosteronemia.

A urinalysis should be performed to rule out proteinuria, a sign of renovascular disease resulting from long-standing **hypertension**. An electrocardiogram can reveal evidence of prior myocardial infarction, arrhythmias, or left ventricular hypertrophy. Its sensitivity for left ventricular hypertrophy is poor, however. In one recent study the sensitivity ranged from 9% to 39%, depending on the criteria used. The specificity was in excess of 90% (21).

Echocardiography is the "gold standard" for diagnosis of left ventricular hypertrophy, but it is not cost-effective for every patient with **hypertension**. If the patient has signs or symptoms of congestive heart failure, echocardiography is indicated to measure left ventricular **systolic** and diastolic function. It is also indicated if the physical examination suggests the presence of valvular heart disease.

Treatment of ISH

Care must be taken not to diagnose ISH on the basis of only one blood pressure reading. Blood pressure should be measured as described previously. If ISH is present on the initial reading, another reading should be taken after the patient has sat quietly for 10 to 15 minutes. If the reading is still elevated, the patient should be given advice regarding diet and exercise. Measures such as salt restriction, weight loss, exercise, and reduction or elimination of alcohol intake have documented efficacy in reducing blood pressure (22). In one study, 52% of hypertensive patients had a reduction in blood pressure to less than 140/90 mm Hg with weight loss and sodium restriction alone (23).

Patients with mildly or moderately elevated blood pressure should be allowed to try lifestyle modification for several months. For those with target-organ damage, as indicated by a history of myocardial infarction, stroke, or renal disease, pharmacologic therapy may need to be instituted sooner than for other patients (table 1).

Table 1. Suggested treatment for patients with isolated systolic hypertension, based on blood pressure and clinical status

Blood pressure stage	Risk group A (no risk factors, no TDD)	Risk group B (≥1 risk factor, no TOD)	Risk Group C (diabetes plus TOD)

High normal (130-139/85-89 mm Hg)	Lifestyle modification	Lifestyle modification	Pharmacologic therapy
Stage 1 (140-159/90-99 mm Hg)	Lifestyle modification (trial of at least several mo)	Lifestyle modification (trial of 2-3 mo)	Pharmacologic therapy
Stages 2 and 3 (≥160/≥100 mm Hg)	Pharmacologic therapy	Pharmacologic therapy	Pharmacologic therapy

TOD, target-organ damage (eg, renal insufficiency, left ventricular hypertrophy, stroke, myocardial infarction).

Adapted from the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Institutes of Health, National Heart, Lung and Blood Institute, 1997 Nov; NIH publication No. 98-4080.

While undergoing lifestyle modification, patients should be encouraged to have their blood pressure checked at home. Ambulatory 24-hour monitoring is available. Ideally, pressure should be measured with a cuff that has a mercury manometer by someone trained in the technique. If this is not feasible, an automated machine may be used. However, the machine should be checked to assure that the measurements obtained correlate with those obtained using a mercury manometer. Patients should be encouraged to keep a log of the measurements obtained at home. This is also an effective means of screening for so-called white coat **hypertension** (that caused by the anxiety of an office visit).

If ISH persists after lifestyle modification and is confirmed by home blood pressure monitoring, pharmacologic therapy is indicated. One of the best initial choices of an antihypertensive for elderly patients is a low-dose, long-acting diuretic, such as 12.5 mg daily of hydrochlorothiazide. This class of medication is inexpensive and, as the SHEP study demonstrated, clearly beneficial in reducing the incidence of cardiovascular events.

Results of the Syst-Eur and STONE studies have demonstrated that a low-dose, long-acting dihydropyridine calcium channel blocker is safe and effective in the elderly population and should now be considered first-line therapy. It or a long-acting diuretic should be the initial drug of choice for patients who require pharmacologic therapy for ISH, unless there is a compelling medical indication for a different class of drug. If the initial dose does not achieve adequate control of blood pressure, the dosage should be slowly increased. If blood pressure is still not optimal, other classes of medications may be carefully added.

Concomitant medical conditions must be taken into account when selecting antihypertensive therapy. For example, if a patient has angina or a history of myocardial infarction, a beta blocker is appropriate. If mild renal insufficiency or cardiomyopathy is present, an angiotensin-converting enzyme inhibitor is a good choice. For a male patient with symptoms of benign prostatic hypertrophy, an alpha blocker would be a reasonable choice.

Difficult-to-control hypertension

In some patients the addition of a second, or even a third, antihypertensive agent is not successful in controlling **hypertension**. In such cases, several diagnostic possibilities other than essential **hypertension** must be considered, ie, true white coat **hypertension**, secondary causes of **hypertension**, and pseudohypertension.

White coat hypertension
White coat **hypertension** should be considered when blood pressure readings are significantly elevated in the absence of target-organ damage. Home blood pressure monitoring is the best way to diagnose this condition. Ambulatory 24-hour monitoring can be useful in determining if a patient's blood pressure rises during other potentially stressful situations. Home readings should be taken by someone trained in the proper technique, preferably using a cuff with a mercury manometer.

Secondary hypertension
A secondary cause of **hypertension** should be suspected when the onset is sudden and severe or when blood pressure levels remain significantly elevated despite the administration of three or four different antihypertensive agents. The most common cause of secondary **hypertension** is chronic renal insufficiency. This is also the easiest to screen for, usually requiring only a simple chemistry profile.

Renal artery stenosis is the next most common cause of secondary **hypertension**. Most cases in the elderly are atherosclerotic in origin. An abdominal bruit that lateralizes to one side should increase suspicion. A renal ultrasound is a good noninvasive screening measure. Renal artery stenosis may be suspected if one kidney is atrophic or smaller than the other. Doppler ultrasound can detect increased velocity in the renal arteries, which is indicative of stenosis. A renal arteriogram is diagnostic. The lesions are quite amenable to angioplasty and stenting. These measures have resulted in significant decreases in blood pressure (24), although data on long-term outcome are lacking.

Other, rare causes of secondary **hypertension** are pheochromocytoma, Cushing's disease, and hyperaldosteronism.

Pseudohypertension
Pseudohypertension is a condition seen almost exclusively in the elderly population. It is the result of calcification and loss of elasticity of the peripheral arteries, which cause patients to have falsely high readings when blood pressure is measured with a cuff. In 1892, Osler noted that such patients have a palpable radial pulse even when the cuff is

inflated above the **systolic** pressure. This means of screening for pseudohypertension, referred to as the Osler maneuver, became widely advocated. However, studies have shown it to be unreliable in identifying patients with pseudohypertension, which seems to be a primarily diastolic phenomenon. In pseudohypertension, cuff measurements of blood pressure underestimate the **systolic** pressure and overestimate the diastolic pressure. Hence, even in patients with pseudohypertension, the mean arterial pressure measured by cuff usually correlates well with the mean arterial pressure measured intra-arterially.

Some preliminary data suggest that blood pressure measurements in the fingers are accurate in patients with pseudohypertension, because these arterioles are not as prone to atherosclerosis as the larger arteries, such as the brachial artery, which is used to auscultate the Korotkoff sounds (25). Pseudohypertension should be suspected in patients with significantly elevated blood pressure readings in both clinical and home settings but no target-organ damage, or in patients who are taking medication and who have significant orthostasis and symptoms of dizziness despite high blood pressure readings. As there are currently no reliable noninvasive screening measures available, intra-arterial monitoring may be necessary to make a definitive diagnosis.

Summary

Isolated systolic hypertension (ISH) is the most common form of **hypertension** in the elderly. It is an even better predictor of morbidity and mortality than is diastolic blood pressure. Several large trials have documented a clear benefit to treating ISH. Therapy should be initiated only after careful evaluation of the patient's overall medical status, because the elderly are at increased risk of adverse effects from medications. Pharmacologic therapy should be started at a low dose and increased slowly, if necessary. If **hypertension** is still present after the addition of two or three medications, a cause other than essential **hypertension** should be considered, such as white coat **hypertension**, secondary **hypertension**, or pseudohypertension.

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Symposium Index

RETURN TO MAY 1, 1999 TABLE OF CONTENTS